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**Published:**

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- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF CERTAIN COMPOUNDS IN TREATMENT OF OBESITY

(57) Abstract: The present invention relates to the use of one or more compound selected from the group of statins, in particular rosuvastatin, atorvastatin, simvastatin, fluvastatin, pravastatin, and terbinafine, interferone alpha-2b, interleukin-4 (IL-4), interleukin-13 (IL-13) and other interleukin-4 receptor agonists, or a functionally equivalent analogue in the manufacture of pharmaceutical preparations for the treatment of obesity, as well as a method for treatment of obesity.



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**TITLE****USE OF CERTAIN COMPOUNDS IN TREATMENT OF OBESITY****DESCRIPTION**

Technical field of the invention

The present invention relates to the use of certain compounds in the manufacture of pharmaceutical preparations and a new method for treatment of obesity, in particular pathological disturbances of regulation of body fat tissue mass and/or obesity associated disorders, such as visceral obesity.

Background art

The metabolic syndrome

It is well recognized that visceral obesity, deranged lipid-lipoprotein profile, including hypertriglyceridemia, hypertension, and insulin resistance are related in a group of metabolic perturbations called the metabolic syndrome. This syndrome is associated with larger risk of cardiovascular disease. So far, a lot of the research on the ethiology of this syndrome has concentrated on neuroendocrine, i.e., hypothalamic, and endocrine disturbances, focusing on the effects of the HPA axis, sex steroids and growth hormone, as well as, of course, insulin (Björntorp, P. Body fat distribution, insulin resistance, and metabolic diseases. *Nutrition* 13, 795-803 (1997). review).

The risk for abdominal obesity and the metabolic syndrome seem to genetically determined to a large extent. According to the thrifty gene hypothesis, genetic selection would favor storage of fat ensure large energy supplies during times of starvation. For several years, several research groups throughout the world have tried to identify thrifty genes. Some of the candidate genes have been detected after identification of genetically obese mouse models (Friedman JM and Halaas JL, Leptin and the regulation of body weight in mammals. *Nature* 395, 763-70, 1998 ).

Under certain circumstances, alcohol also enhances visceral obesity and increased serum triglyceride levels, i.e., manifestations of the metabolic syndrome.

Understanding obesity

Obesity is a large problem in the Western world since both severe and moderate obesity is associated with increased health risks. Obesity is associated with diseases such as diabetes, hypertension and heart disease, whose incidence increases with body-mass

Index (BMI, body mass in kg/square of height in meters). A study based on information on 18-year-old Swedish military conscripts show a 1.4-fold increase in prevalence of overweight (BMI >25) and a 1.7-fold increase in obesity (BMI >30) from the year 1971 to 1993 (Rasmussen F, Johansson M and Hansen HO, 1999).

Generally, obesity is due to energy intake that greater than energy expenditure. This can be caused by overeating, i.e. higher food intake than necessary for maintenance of body mass. In addition, low mobility and low metabolic rate may predispose for obesity (see Flier, J. S. and Foster D. W. (1998) Eating disorders: obesity, anorexia nervosa, and bulimia nervosa. In: Williams Textbook of Endocrinology, 9th Ed, Saunders Co.).

However, the general opinion that obesity is largely the result of a lack of willpower is unsatisfactory. Intense research efforts are therefore made to reveal the genetic and environmental factors of importance for development of obesity (Friedman JM and Haas JL, 1998).

Obesity in humans and mice

Animal models can be used for investigating which genes that are causing development of obesity. Of particular importance is the information that can be gained from mouse strains that develop obesity because of gene knockouts. These mouse strains can provide evidence that a certain gene product is of crucial importance for regulation of body fat. This in turn may facilitate the development of new treatment paradigms. There are indications that there are gender differences regarding the genetic etiology of obesity (see e.g. Costet, P. et al. (1998) Peroxisome Proliferator-activated receptor  $\alpha$ -isoform deficiency leads to progressive dyslipidemia with sexually dimorphic obesity and steatosis. *J. Biochem. Chem.* 273,29577-29585).

Obesity and blood fats in relation to cardiovascular disease

It is recognized that obesity, especially visceral obesity, and deranged lipid-lipoprotein profile, including hypertriglyceridemia and hypercholesterolemia are associated with larger risk of cardiovascular disease (Lamarche B, et al. (1998), Visceral obesity and the risk of ischemic heart disease: insights from the Quebec cardiovascular study. *Growth hormone and IGF research* 8, (suppl. B) 1-8.). So far, a lot of the research on the etiology of this syndrome has dealt with neuroendocrine, i.e. hypothalamohypophyseal, and endocrine disturbances, focusing on the effects of the hypothalamus-pituitary-adrenal (HPA) axis regulating glucocorticoid, sex steroids and growth hormone (see e.g. Björntorp, P. (1996) The regulation of adipose tissue distribution in humans, *Int. J. Obesity* 20, 291-301.)

Obesity and obesity-related disorders are thus among the leading causes of illness and mortality in the developed world (Kopelman PG, 2000, "Obesity as a medical problem", Nature 404: 635-43). Parts of the brain, including specific regions of the hypothalamus and the brain stem, are involved in the regulation of feeding and body fat mass  
5 (Friedman JM, Halaas JL, 1998, "Leptin and the regulation of body weight in mammals", Nature 395: 763-70; Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG, 2000, "Central nervous system control of food intake", Nature Apr 6; 404 (6778): 661-71).  
The regulation of feeding and body mass by the hypothalamus is influenced e.g. by the  
10 adipose tissue derived hormone leptin.

#### Summary of the invention

The aim of the present invention is to provide new medical products and methods for treatment of obesity.

15

More precisely, the invention relates to the use of certain substances for the production of a pharmaceutical preparation that upon administration to a patient reduces adipose tissue mass for treatment of obesity, in particular visceral obesity.

20 Furthermore, the invention relates to a method for treatment of obesity wherein a pharmaceutically effective amount of a certain substance that upon administration to a patient for reducing adipose tissue mass.

#### Detailed description of the invention

25 In the research work leading to the present invention it was found that treatment with one or more of the compounds selected from the group consisting of statins, in particular atorvastatin, simvastatin, fluvastatin, pravastatin, and terbinafine, and interferon alpha-2b or a "functionally equivalent analogue" selectively can decrease body fat.

30 Further, it has been observed that interelukin-4 (IL-4) and interleukin-13 (IL-13), i.e. two interleukins that act on IL-4 receptors, will decrease body fat mass.

Based on this finding, it is proposed that IL-4, IL-13 and other IL-4 receptor agonists are used to treat obesity and obesity related diseases.

35

The invention thus relates to medicinal products comprising a substance that upon administration to a patient leads to reduced obesity.

The expression "functionally equivalent analogue" used herein relates to any substance that is structurally similar to the compounds of the group given above and has essentially the same pharmacological and/or therapeutical effects.

- 5 The term "patient" used herein relates to any human or non-human mammal in need of treatment with the pharmaceutical preparation or method according to the invention.

Patients particularly suitable for treatment according to the invention are patients suffering from the metabolic syndrome.

10

The term "treatment" used herein relates to both treatment in order to cure or alleviate a disease or a condition, and to treatment in order to prevent the development of a disease or a condition. By "chronic treatment" is meant treatment that continues for more than two weeks.

15

The medicinal product and the method according to the invention are suitable for treatment of different pathological disturbances of regulation of body adipose tissues. More precisely, the medicinal product and the method according to the invention are suitable for treatment of obesity and overweight by reducing adipose tissue mass.

20

Obesity includes visceral or general obesity that is due to genetic predisposition, a condition sometimes described as the thrifty genotype. Obesity caused by lifestyle and environment, such as lack of exercise, or diets with high caloric content or high fat content, can also be treated as described herein. The medicinal product and the method according to the invention could also be used to enhance the effects of exercise and/or diet. Obesity is often associated with resistance to leptin treatment. Visceral obesity includes obesity in the abdominal cavity, in and around the liver, as well as abdominal muscle fat.

25

- 30 The reduction in adipose tissue mass according to the invention preferably results in a weight reduction that is larger than 3%, preferably larger than 5% of the body weight at the start of treatment.

#### Experimental

- 35 In order to show the fat reducing effect of statins the following experiment was carried out.

Addition of 1 mM of fluvastatin suppresses fat content in the worm *C. elegans*. The statin fluvastatin was added to the medium of an agar plate with *C. elegans*, and the fat con-

- tent of intestinal cells was found to be reduced in the worm, presumably after it has ingested the fluvastatin, a so called statin, a group of substances known to inhibit HMG Co A reductase. The worms do not have visceral and subcutaneous fat cells in a similar way as higher organisms. Instead they store fat droplets in intestinal cells and hypodermal cells. As the worm is transparent the fat can easily be visualised with Nile Red fat staining as shown in the attached FIG. 1, wherein the left image shows the *C. elegans* control, i.e., a situation prior to treatment with fluvastatin, and the right image shows the result after treatment with fluvastatin.
- 10 The medicinal product or pharmaceutical composition or pharmaceutical preparation according to the invention may also comprise other substances, such as an inert vehicle, or pharmaceutical acceptable adjuvants, carriers, preservatives etc., which are well known to persons skilled in the art.
- 15 Said substance according to the invention is preferably formulated in a form enabling passage of the certain compound of the group given.
- Said substance can be administered subcutaneously, intramuscularly, intravenously, intraperitoneally, intranasally or orally.
- 20 The substance according to the invention is preferably administered in a dose of 0.1 mg to 200 mg per kg body weight per day or alternatively 5 000 to 500 000 International Units per kg body weight per day.
- 25 Furthermore, the invention relates to a method for chronic treatment of obesity wherein a pharmaceutically effective amount of a compound of the group given that upon administration to a patient is administered to said patient for reducing adipose tissue mass.
- 30 In the method according to the present invention, a "pharmaceutically active amount" of the substance is used. This expression relates to a dose of the substance that will lead to the desired pharmacological and/or therapeutic effect. The desired pharmacological and/or therapeutic effect is, as stated above, to cure or alleviate different pathological disturbances of regulation of body adipose tissues, leading to obesity, i.e. treatment of
- 35 obesity and overweight by reducing adipose tissue mass.

The compounds of the present invention can be administered in the form of oral, rectal, injection, or inhalation preparations. Oral compositions normally exist as tablets,

- granules, capsules (soft or hard), or powders, either coated or uncoated products. As coated products they may be merely enteric coated to provide for a more readily administered preparation, or as a sustained release coated composition, where the release of active compound will take place due to the dissolution of the coating, which dissolution is dependent on where in the gastro-intestinal tract one will have a release. Thus the release can be controlled as to place and time. It may also be advantageous to coat the active compound if this is subject to degradation, such as by gastric acid, in order then to have the compound to pass the stomach.
- 10 Tablets and capsules normally contain one dose of the active compound, i.e., the dose determined to fulfil the requirements of obtaining a therapeutically active level in serum or otherwise, either this is required once, twice or more times a day (24 hrs).
- 15 Rectal compositions are normally prepared as suppositories, where the active compound is dissolved or dispersed in a waxy compound or fat having a melting temperature in the range of the body temperature, as to release the active compound when administered rectally.
- 20 Preparations for injection are commonly made for subcutaneous, intramuscular, intravenous, or intra peritoneal administration. Injection solutions are normally provided with an adjuvant to facilitate absorption of the active compound.
- 25 Preparations for inhalation are commonly present as powders which are administered either in pressurized containers with a dosing nozzle, or in an inhaler system where the powder is dosed in the system and then the patient is inhaling air through the apparatus to such degree that the powder becomes airborne and enters the respiratory tract, including the lungs. Inhalation preparations are normally used for inflammatory conditions in the respiratory tract including the lungs.
- 30 The compositions contain 0.5 to 99 % by weight of active compound, and the remainder is different inert, non-therapeutically active compounds which facilitate administration, preparation such as granulation, tableting, or storage. Such inert materials may, however, have an administratively positive effect.
- 35 The active compounds of the invention is administered in an amount of 0.1 to 200 mg or 5 000 to 500 000 International Units per kilogram body weight depending on the condition of the patient, route of administration, age and body weight of the patient, and other considerations made by the physician. The most important aspect hereby is

the serum concentration which may be 0.1 to 100 mM of active compound, in accordance with present findings.

Furthermore, it is possible to combine the treatment according to the invention with  
5 other conventional pharmacological treatments of obesity. The substance according to the invention may thus be administered in combination with other conventional pharmaceuticals used to treat obesity.



**CLAIMS**

1. Use of one or more of the compounds selected from the group consisting of statins, in particular rosuvastatin, atorvastatin, simvastatin, fluvastatin, pravastatin, and terbinafine, interferon alpha-2b, interleukin-4 (IL-4), interleukin-13 (IL-13) and other  
5 Interleukin-4 (IL-4) receptor agonists, or a "functionally equivalent analogue" in the manufacture of a pharmaceutical preparation for the treatment of obesity.
2. Use according to claim 1, wherein the pharmaceutically active compound is selected from the group of statins.  
10
3. Use according to claim 1, wherein the pharmaceutically active compound is atorvastatin.
4. Use according to claim 1, wherein the pharmaceutically active compound is  
15 simvastatin.
5. Use according to claim 1, wherein the pharmaceutically active compound is fluvastatin.
- 20 6. Use according to claim 1, wherein the pharmaceutically active compound is pravastatin.
- 7 Use according to claim 1, wherein the pharmaceutically active compound is rosuvastatin.  
25
8. Use according to claim 1, wherein the pharmaceutically active compound is terbinafine.
9. Use according to claim 1, wherein the pharmaceutically active compound is interferon  
30 alpha-2b.
10. A method according to claim 1, wherein the pharmaceutically active compound is IL-4.
- 35 11. Use according to claim 1, wherein the pharmaceutically active compound is IL-13

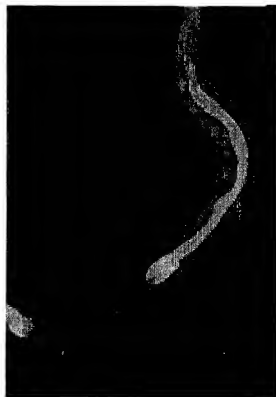
12. Use according to claim 1, wherein the pharmaceutically active compound is an IL-4 receptor agonist other than IL-4 and IL-13.
13. Use according to claims 1-12, wherein the pharmaceutically active compound is a functionally equivalent analogue thereof.
14. Use according to claim 1, wherein said obesity is visceral or general obesity that is due to genetic predisposition.
15. Use according to claim 1, wherein said obesity is caused by lifestyle or environment.
16. Use according to claim 1, wherein said obesity is a symptom of the metabolic syndrome.
17. Use for chronic treatment of obesity wherein a pharmaceutically effective amount of one or more of the compounds selected from the group consisting of statins, in particular rosuvastatin, atorvastatin, simvastatin, fluvastatin, pravastatin, and terbinafine, interferon alpha-2b, interleukin-4 (IL-4), interleukin-13 (IL-13) and other Interleukin-4 (IL-4) receptor agonists, or a "functionally equivalent analogue" thereof is administered to said patient for reducing adipose tissue mass.
18. A method for treatment of obesity wherein a pharmaceutically effective amount of one or more of the compounds selected from the group consisting of statins, in particular rosuvastatin, atorvastatin, simvastatin, fluvastatin, pravastatin, and terbinafine, interferon alpha-2b, and interleukin-4 (IL-4), Interleukin-13 (IL-13) and other Interleukin-4 (IL-4) receptor agonists, or a "functionally equivalent analogue" thereof is administered to said patient for reducing adipose tissue mass.
19. A method according to claim 18, wherein the pharmaceutically active compound is selected from the group of statins.
20. A method according to claim 18, wherein the pharmaceutically active compound is atorvastatin.
21. A method according to claim 18, wherein the pharmaceutically active compound is simvastatin.

22. A method according to claim 18, wherein the pharmaceutically active compound is fluvastatin.
23. A method according to claim 18, wherein the pharmaceutically active compound is pravastatin.
24. A method according to claim 18, wherein the pharmaceutically active compound is rosuvastatin.
25. A method according to claim 18, wherein the pharmaceutically active compound is terbinafine.
26. A method according to claim 18, wherein the pharmaceutically active compound is interferon alpha-2b.
27. A method according to claim 18, wherein the pharmaceutically active compound is IL-4.
28. A method according to claim 18, wherein the pharmaceutically active compound is IL-13.
29. A method according to claim 18, wherein the pharmaceutically active compound is an IL-4 receptor agonist other than IL-4 and IL-13.
30. A method according to claims 18-29, wherein the pharmaceutically active compound is a functionally equivalent analogue thereof.
31. A method according to claim 18, wherein said obesity is visceral or general obesity that is due to genetic predisposition.
32. A method according to claim 18, wherein said obesity is caused by lifestyle or environment.
33. A method for chronic treatment of obesity wherein a pharmaceutically effective amount of one or more of the compounds selected from the group consisting of statins, in particular rosuvastatin, atorvastatin, simvastatin, fluvastatin, pravastatin, and terbinafine, interferon alpha-2b, interleukin-4 (IL-4), interleukin-13 (IL-13) and other

interleukin-4 (IL-4) receptor agonists, or a "functionally equivalent analogue" thereof is administered to said patient for reducing adipose tissue mass.

1/1

Control



Fluvastatin 1 mM



Fig.1

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2003/001913

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/505, A61K 31/40, A61K 31/351, A61K 31/405, A61K 31/22, A61K 31/137, A61K 38/20, A61P 3/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, MEDLINE DATA, EMBASE, BIOSIS DATA, WPI DATA, EPO-INTERNAL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|-----------|---|-----------------------|
| A         | Am J. Cardiol, Volume 87, 2001, Anders G. Olsson,<br>"Statin Therapy and Reductions in Low-Density<br>Lipoprotein Cholesterol: Initial Clinical Data on<br>the Potent New Statin Rosuvastatin", pages 33B-36B<br><br>-- | 1-7,13-24,<br>30-33   |
| A         | WO 9803069 A1 (BRISTOL-MYERS SQUIBB COMPANY),<br>29 January 1998 (29.01.1998)<br><br>--<br>-----  | 1-7,13-24,<br>30-33   |

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

8 April 2004

Date of mailing of the international search report

15-04-2004

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 2003/001913**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **17-33**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see extra sheet**
2. ☒ Claims Nos.: **1, 12, 17-18, 29, 33 (all partially)**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**see extra sheet**
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

**see extra sheet**

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
**1 partially, 2-7, 13-18 partially, 19-24 and 30-33 partially.**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 2003/001913

## Box II.1

Claims 17-33 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

## Box II.2

The expression "interleukin-4 receptor agonist" in claims 1, 12, 17-18, 29 and 33 defines the compounds by reference to a desirable property. The claims cover all compounds having this property whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed which are mainly those parts relating to the compounds interleukin-4 and interleukin-13.

## Box III

The present application comprises 4 inventions, namely:

- 1) Use of statins for the treatment of obesity. Claims 1 partially, 2-7, 13-18 partially, 19-24 and 30-33 partially.
- 2) Use of terbinafine for the treatment of obesity. Claims 1 partially, 8, 13-18 partially, 25 and 30-33 partially.
- 3) Use of interferone alpha-2b for the treatment of obesity. Claims 1 partially, 9, 13-18 partially, 26 and 30-33 partially.
- 4) Use of interleukin-4, interleukin 13 and other interleukin-4 receptor antagonists for the treatment of obesity. Claims 1 partially, 10-12, 13-18 partially, 27-29 and 30-33 partially.

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 2003/001913

According to PCT Article 34 (3) (a-c) and Rule 13.2 the invention shall relate to one invention only or to a group of inventions that are based on a common inventive matter. In order to fulfil the demands of unity of PCT Article 34 (3) (a-c) and Rule 13.2 a technical connection between all the inventions comprised by the application, the connection consisting in one or more common or corresponding special technical feature, has to be present. A special technical feature refers to such technical features that define a contribution which each of the inventions makes over the prior art.

The application discloses 4 inventions, which are considered to lack common technical features apart from the prior art for the following reasons:

The invention is concerned with the problem of providing novel pharmaceutical preparations for the treatment of obesity. The application comprises 4 types of substances which all solve this problem. Pharmaceutical preparations for the treatment of obesity are previously known and in order to be considered as one invention with at least one technical feature apart from the prior art in common, the substances as such need to exhibit a common technical feature. The groups of substances in the application do not have such a common feature in their structure or in their mechanism of their mechanism of function. Hence the demands of unity of PCT Article 34 (3) (a-c) and Rule 13.2 is not fulfilled.

Only invention 1 according to above has been searched

INTERNATIONAL SEARCH REPORT  
Information on patent family members

27/02/2004

International application No.

PCT/SE 2003/001913

|    |   |         |    |            |    |            |   |            |
|----|---|---------|----|------------|----|------------|---|------------|
| WO | . | 9803069 | A1 | 29/01/1998 | AU | 716145     | B | 17/02/2000 |
|    |   |         |    |            | AU | 3662497    | A | 10/02/1998 |
|    |   |         |    |            | CA | 2260995    | A | 29/01/1998 |
|    |   |         |    |            | EP | 1014791    | A | 05/07/2000 |
|    |   |         |    |            | JP | 2000515526 | T | 21/11/2000 |
|    |   |         |    |            | US | 5883109    | A | 16/03/1999 |
|    |   |         |    |            | ZA | 9705950    | A | 04/01/1999 |

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